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Central Venous Catheter Infection by *Aspergillus fumigatus* in a Patient With B-Type Non-Hodgkin Lymphoma

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Invasive *Aspergillus* infection is still a major problem in immunocompromised patients. A central venous catheter infection by *Aspergillus fumigatus,* however, has not yet been reported. We describe the case of a 10-year-old female patient with B-type non-Hodgkin lymphoma treated according to the German chemotherapy protocol NHL-BFM 90. Isolation of *Aspergillus fumigatus* from the blood was the first hint of invasive aspergillosis. A central venous catheter-associated infection was suggested, since *Aspergillus* was also isolated from the thrombotic tip of the removed catheter. Secondary pulmonary aspergillosis was documented radiologically. The patient was treated successfully by Amphothericin B and Itraconazol and explantation of the central venous catheter under conditions of complete hematopoietic regeneration of the bone marrow with omission of the final chemotherapeutic cycle. © 1996 Wiley-Liss, Inc.

Key words: invasive aspergillosis, central venous catheter-associated infection by *Aspergillus fumigatus,* hematopoietic regeneration

INTRODUCTION

Invasive aspergillosis is one of the most dangerous complications of myelosuppressive chemotherapy especially for hematological malignancies in both adults and children. Infection rates in these patient groups have been reported between 5% and 60%. Published series from the last two decades indicate an overall mortality rate of above 50%, despite therapy with Amphothericin B [1–8]. Seventy percent of patients that are neutropenic for a period longer than 30 days are reported as having developed invasive aspergillosis [9]. Only in rare cases can *Aspergillus* be cultured from the blood stream. To our knowledge, no case of a primary central venous catheter-associated infection by *Aspergillus fumigatus* has yet been described.

We report on a pediatric oncology patient with invasive pulmonary aspergillosis following a central venous line infection and discuss the clinical course in view of the literature.

CASE REPORT

A 9.5-year-old girl with a stage IV non-Hodgkin lymphoma of Burkitt-type was treated according to the German protocol NHL-BFM 90 for high risk patients. Prior to therapy a central venous catheter (*Groshong*) was implanted. Complete remission was documented after two of six chemotherapeutic cycles. Following each treatment cycle, the patient developed fever during the period of granulocytopenia and was treated with antibiotics and interventional Granulocyte Colony-Stimulating Factor (G-CSF). Likewise, after the third chemotherapeutic cycle a febrile episode responded promptly to antibiotic treatment. *Aspergillus spec.,* however, was cultured from the blood drawn via the central venous catheter. In view of the otherwise favorable clinical course, the culture was interpreted as a laboratory contamination. Shortly thereafter, there were two episodes of thrombotic occlusion of the central venous catheter which responded to fibrinolytic therapy. Following the fifth chemotherapy cycle, the girl developed another febrile episode, although the white blood cell count (WBC) was recovering from its nadir. She was moderately ill and had a mild cough. C-reactive protein was slightly elevated (14 mg/L). The conventional chest radiograph was normal and serological parameters were negative (Table I). After four days of remittent fever despite antibiotic treatment, the central venous catheter was removed. In the meantime, results from the initial blood cultures yielded growth of *Aspergillus fumigatus,* as did cultures from the thrombotic tip of the centralvenous catheter. The girl's cough worsened, and she complained about chest pain. Computer tomography (CT) of the lungs (Fig. 1) showed signs of invasive aspergillosis, and so

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TABLE I. Time Course of Aspergillus Serology*

Days (after onset of chemotherapy)	Serological tests						
	Hemagglutination	Immunodiffusion					Antigen
		A.fum.	A.fla.	A.nid.	A.nig.	A.ter.	A. spec.
3	1:10	neg	neg	neg	neg	neg	–
16	1:10	neg	neg	neg	neg	nge	–
22	1:10	neg	neg	neg	neg	neg	–
36	1:10	neg	neg	neg	neg	neg	–
Positive blood culture (day 63)							
72	1:20	neg	neg	neg	neg	neg	–
109	1:20	neg	neg	neg	neg	neg	–
Positive blood culture (day 109, day 111)							
116	**1:80**	neg	neg	neg	neg	neg	–
117	**1:160**	neg	neg	+/–	neg	neg	–
129	**1:160**	**pos**	+/–	**pos**	neg	+/–	–
131	**1:80**	**pos**	+/–	**pos**	neg	+/–	–
137	**1:80**	**pos**	**pos**	**pos**	neg	+/–	–
162	**1:40**	neg	neg	neg	neg	neg	–
235	1:10	neg	neg	neg	neg	neg	–

*Cut-off for hemagglutination test: 1:80.

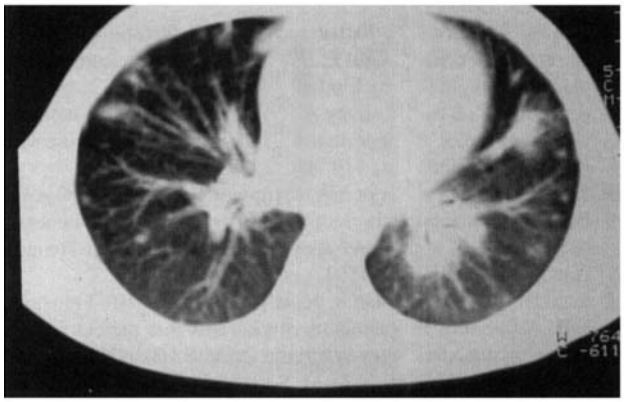

Fig. 1. Computer tomography of the lungs, 11 days after the first positive blood culture had been taken. Multiple, nodular and cuneiform infiltrates measuring about 2 cm can be seen in both lungs.

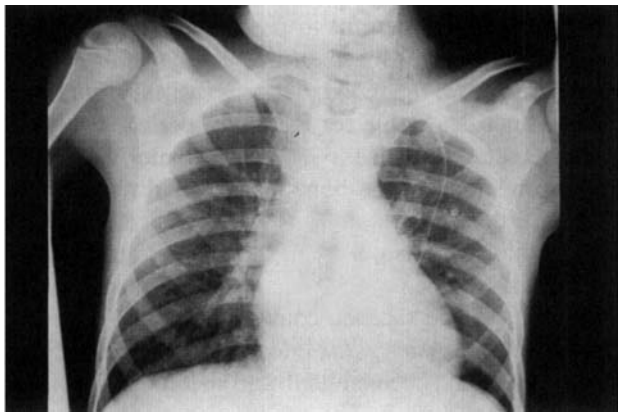

Fig. 2. Radiograph of the lungs, 18 days after first positive blood culture.

did the conventional chest radiograph for the first time 18 days after diagnosis (Fig. 2). Ultrasound examination of the heart gave no evidence of cardiac involvement. Treatment with Amphothericin B was started immediately. The scheduled next and last chemotherapeutic cycle was omitted. The girl's clinical and radiological status improved during the course of antimycotic therapy. A high dose of Amphothericin B (1.25 mg/kg/d) was continued for 36 days with relevant side effects, such as chills, fever, hypotension and tubular damage of the kidneys. Thereafter, Amphothericin B was replaced by Itraconazol for outpatient treatment and was continued for a total of about 4 months of antimycotic therapy. One year after the diagnosis of aspergillosis, the patient is well with respect to both lymphoma and *Aspergillus* infection. The lungs have recovered completely, and the kidney function has normalized.

DISCUSSION

A positive culture of *Aspergillus spec.* from the blood is a rarity. To our knowledge only 12 very heterogenous cases have been reported [10–19], with only 4 cases in pediatric oncology [10,11]. In a single case, the results of the blood cultures were, as in our patient, indicative of invasive pulmonary aspergillosis [19].

To our knowledge, a primary central venous catheter-associated infection has not yet been described. Primary cutaneous aspergillosis has been associated with Hickman intravenous devices. Two patients with primary cutaneous aspergillosis are reported as having *Aspergillus flavus*

also isolated from the tip of the central venous catheter [20]. One of them survived under conditions of hematopoietic regeneration. In our patient, a central venous catheter-associated infection was suggested for the following reasons: *Aspergillus fumigatus* had been cultured from the blood as well as from the tip of the explanted catheter; the central venous catheter had been occluded several times by thrombotic material; the clinical course was initially moderate and characterized by remittent febrile episodes only in addition to a mild cough, and finally, after the removal of the catheter, fever had disappeared promptly. Invasive aspergillosis of the lungs might have been the result of multiple septic thromboembolies from the tip of the infected central venous catheter. Chest CT scan showed signs of beginning invasive aspergillosis for the first time 11 days after the positive blood culture, conventional chest radiographs for the first time 18 days after establishing the diagnosis of aspergillus infection.

Definitive diagnosis of invasive aspergillosis is difficult and usually established postmortally. Cultural, serological and imaging methods are rarely helpful to come to an early diagnosis. As described in our case, serologic markers were not helpful to predict aspergillosis. They became positive for the first time 8 days after culturing *Aspergillus* from the blood, whereas the *Aspergillus* antigen was not detectable for the entire period.

Besides removal of the infected catheter, hematopoietic regeneration of the bone marrow and reconstitution of cellular defense mechanisms was of critical importance for the clinical course in our patient. Fever and fungemia had appeared when the WBC was yet recovering from the nadir and had reached counts above 2,000/μL. As a consequence of *Aspergillus* infection, the last chemotherapeutic cycle had been omitted, and so the WBC remained within normal ranges. The patient survived under treatment with Amphothericin B and subsequent oral Itraconazol.

In one clinical study [2], duration and dose of antifungal therapy were not significantly different between survivors and nonsurvivors of aspergillosis, which underlines the overall importance of the patient's own hematopoietic regeneration. Without this recovery, invasive aspergillosis is still a fatal infectious disease.

In conclusion, we wish to emphasize that *Aspergillus* central line infections have to be taken into consideration in oncology patients, especially in the case of thrombotic occlusion of the catheter. Antimycotic treatment by Amphothericin B and Itraconazol can be effective under conditions of regeneration of the bone marrow.

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